AD_____

Award Number DAMD17-98-1-8503

TITLE: Daily 1 α-OH-D_2 in Hormone Refractory Prostate Cancer: Assessment of Clinical and Biochemical Effects

PRINCIPAL INVESTIGATOR: Howard H. Bailey, M.D.

CONTRACTING ORGANIZATION: University of Wisconsin
Madison, Wisconsin 53792

REPORT DATE: August 1999

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 1999	Annual (1 Aug 98 – 31 Jul 99)

4. TITLE AND SUBTITLE

Daily 1 α-OH-D_2 in Hormone Refractory Prostate Cancer: Assessment of Clinical and Biochemical Effects

5. FUNDING NUMBERS

DAMD17-98-1-8503

6. AUTHOR(S)

Howard H. Bailey, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Wisconsin
Madison, Wisconsin 53792

E-Mail: hhbailey@facstaff.wisc.edu

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 Words)*

Vitamin D and its metabolites via binding to cellular vitamin D receptors principally regulate bone homeostasis, but also have been observed to be potent growth inhibitors of neoplastic cells. Preclinical work has strongly implied vitamin D-based therapy could be effective in prostate cancer. Early clinical work with vitamin D has been complicated by its significant calcemic effects. 1α-OH-D_2 is a vitamin D analog with less calcemic effects but significant growth inhibitory effects. Objective anti-tumor activity was observed in a prostate cancer patient during an initial phase I study of 1α-OH-D_2. We are performing a phase II study of daily 1α-OH-D_2 in patients with advanced androgen-independent prostate cancer. We have observed transient mild hypercalcemia without symptoms in selected patients. No objective tumor responses have been observed to date and the study is too early to discuss the primary endpoint of time-to-treatment failure. Pilot correlative studies evaluating plasma transforming growth factor β1 levels and T cell receptor-associated signal transducing ζ chain expression in peripheral mononuclear cells in patients undergoing study participation are underway without significant preliminary data. Observations to date continue to support the possibility that therapy with daily 1α-OH-D_2 in androgen-independent prostate cancer could be effective.

14. SUBJECT TERMS

Prostate Cancer
Clinical Trials, Vitamin D

15. NUMBER OF PAGES

8

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

_____ Where copyrighted material is quoted, permission has been obtained to use such material.

_____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

_____ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

_NA_ In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

_✓_ For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

_NA_ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

_NA_ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

_____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

H Barclay 8-26-99

PI - Signature Date

Table of Contents

Introduction

The finding of vitamin D receptors (VDRs) in many different cells, including normal and malignant prostate cells, and the corresponding observation in these same cells that vitamin D metabolites can regulate cell growth and promote differentiation via VDRs has strongly implied a potential role for these metabolites in cancer prevention or therapy. Epidemiologic studies and *in vitro* studies observing physiologic levels of vitamin D ($1\alpha,25(OH)_2D_3$) inhibiting proliferation of prostate cancer cells support this implication. The clinical development of vitamin D metabolites/analogs has been slowed by their calcemic activity. 1α-OH-D_2 is an analog with significantly less calcemic activity than $1\alpha,25(OH)_2D_3$ but with similar potency in inhibiting cancer cell proliferation. It has been administered chronically to osteopenic patients without serious sequelae and has recently undergone phase I testing (daily, oral 1α-OH-D_2) in hormone refractory prostate cancer patients. Transient grade 1 or 2 hypercalcemia was dose-limiting at 12.5 to 15 μg/day. Objective evidence of anti-tumor activity was observed in one patient and multiple other patients had stable disease lasting > 6 months. Based on these preliminary data a phase II study of daily (12.5 μg/day) 1α-OH-D_2 in hormone refractory prostate cancer patients was recently begun. The primary endpoint is time-to-disease progression and survival. Two main pilot correlative studies are being performed, measurement of plasma $TGF\beta_1$ levels and T cell receptor (TCR)-associated signal transducing ζ chain expression in PBLs in patients before, during and after 1α-OH-D_2 therapy. These assays will hopefully provide insight into 1α-OH-D_2 mechanistic issues and/or provide surrogate markers of clinical benefit secondary to 1α-OH-D_2. Additional correlative studies include assessment of VDR status in patient tissue blocks, PSA determinations, and evaluation of bone turnover markers. Nine patients have been entered to date with 2 patients still on study with stable disease at 6 and 2 months. No unexpected toxicities have been observed. Pilot correlative study data is being collected but has not been analyzed to date. Patient enrollment continues. The preliminary data strongly suggest hormonal therapy with vitamin D analogs could be an effective therapy for hormone refractory prostate cancer, which currently has no proven effective therapy.

Body

Review of Statement of Work

Task 1 (Aim 1)	Phase II study of 1α-OH-D_2 in androgen-independent prostate cancer patients.
Months 1 – 24:	Patient recruitment, enrollment and study participation
Months 24-30:	Continued patient follow-up, data interpretation
Tasks 2 & 3 (Aims 2 & 3)	Pilot study of laboratory correlates.
Months 1 – 24:	Assay performance
Months 24-30:	Data interpretation

Year 1 (Months 1-12)
Task 1 Phase II study of 1α-OH-D_2 in androgen-independent prostate cancer patients.

The study did not obtain all final administrative approvals until January 1999. Study accrual began with the recommended phase II dose of 12.5 μg/day of 1α-OH-D_2. Nine patients have been accrued through the January 1999 through July 1999. Two patients are still active with stable disease at 6 and 2 months of study participation. Seven patients were removed from study with progressive disease per bone scan or CT scan. They were onstudy for 1 – 7 months. No objective responses have been observed. Transient grade 1 hypercalcemia has been observed in 5 of 9 patients. ***N.B.*** Due to safety concerns, any degree of hypercalcemia is considered dose-limiting and requires study drug discontinuation followed by a dose reduction when the hypercalcemia resolves. There has been no occurrence of symptomatic hypercalcemia. Only 1 of 9 enrolled patients has died. This patient died of progressive disease 3 months after stopping study drug. Patient enrollment continues at the expected rate.

The projected goal was approximately 20 patients per year. From the start of the protocol we are on schedule, from the start of the grant period (3 months earlier) we are slightly behind. No changes are planned in patient recruitment.

Relative to the hypothesis of vitamin D based therapies becoming an additional effective hormonal therapy, no conclusions can be drawn.

Task 2&3. Laboratory Correlative Studies.

One of the main goals of the correlative studies is to explore potential ways of predicting likelihood of benefit either before or early in vitamin D-based therapy in androgen-inpendent prostate cancer patients. The studies listed below are being evaluated for that purpose and due to the possibility prostate-specific antigen (PSA) levels will be misleading.

Plasma transforming growth factor β_1 (TGFβ_1). Prior preclinical work with vitamin D analogs has noted an association between increased expression of the negative growth factor TGFβ and growth inhibition. We are examining serial plasma TGFβ_1 in patients undergoing therapy with 1α-OH-D_2 in order to assess any possible mechanistic relationships but also to determine if plasma TGFβ_1 levels during 1α-OH-D_2 therapy could antedate objective clinical responsiveness. These samples have been collected and the assays are being run. No preliminary data is available.

Expression of Signal-transducing ζ Chains in peripheral T and NK cells. Evaluation of T cell receptors (TCR), primarily ζ chain, has been correlated with disease state in prostate cancer patients as well as other malignancies. Vitamin D also has been implicated in multiple immune mediated activities. As with TGFβ, we are assessing ζ chain TCR status as a possible mechanistic and predictive laboratory correlate. We have been collecting whole blood samples and separating peripheral mononuclear cells by ficoll-

hypaque gradient. Flow cytometric evaluation of TCR-ζ status is ongoing with very preliminary data available which has not been analyzed. No obvious early trends indicative of 1α-OH-D_2 clinical effects are evident.

Bone turnover markers. Serum osteocalcin and urinary levels of hydroxyproline are indirect measures of osteoblastic activity and bone resorption. These studies were proposed to better understand the effects of vitamin D-based therapy on bone metabolism. These studies are being collected but have not been run/analyzed to date.

Vitamin D receptor status (VDR). It is hypothesized the growth inhibitory effects of 1α-OH-D_2 are via interaction VDR and the eventual downstream effects of this interaction. Therefore, similar to antiestrogens in breast cancer and antiandrogens in prostate cancer, determination of the specific receptor status can be helpful in predicting clinical benefit. Paraffin blocks from primary tumor biopsies are being collected, when available. No ligand-binding studies have been performed to date.

Key Research Accomplishments

The project is moving forward as predicted with expected accrual rates and ongoing data collection. No key research accomplishments have been noted to date.

Reportable Outcomes

None.

Conclusions

Patient accrual continues on the Phase II study of daily 1α-OH-D_2 in androgen-independent prostate cancer patients. The early experience with the study reinforces the concept that vitamin D-based therapy can be given safely to prostate cancer patients and the main/exclusive toxicity is transient hypercalcemia. The remaining important issue this study plans to address is whether clinical benefit is derived from vitamin D-based therapy, in this case with 1α-OH-D_2. We have noted a high rate (4/9) of grade 1 hypercalcemia, which per protocol requires a dose reduction. Therefore many patients are not being treated at the initial recommended phase II dose of 12.5 μg/day. This increased incidence of required dose reductions is due to not allowing any hypercalcemia during the phase II study as compared to allowing grade 1 hypercalcemia during the phase I study. This change was incorporated due to concerns regarding associated renal toxicity with grade 2 hypercalcemia encountered towards the end of the phase I study (after submission/approval of this DOD project). No conclusions can yet be made regarding the clinical viability of 1α-OH-D_2 in prostate cancer.

The laboratory correlative studies are ongoing as well, without any meaningful preliminary data at this time. No difficulties have been encountered or are expected in regards to collecting or performing these studies. Again, the main issue is whether they will have any clinical significance.

The ongoing value of this project mainly pertains to the novelty of the therapeutic area as well as the study design itself. As mentioned above, the study continues to prove vitamin D analogs can be given safely to prostate cancer patients at levels greater than vitamin D can be administered. This is significant not only in the arena of therapeutics but also in the area of chemoprevention. Vitamin D-based therapies are of great interest in the prevention of many cancers. This is also significant for other cancer types. Another potential important area this study is exploring, "Is whether mechanistic correlates can be early predictors of clinical benefit?" This is an important area, since most "cytostatic" agents are frequently given for many months before an assessment for clinical benefit is made. If this study were to determine prestudy correlative values or correlative effects during the first few weeks of therapy were predictors for eventual clinical benefit, the value of these findings is self-explanatory.

References

None.

Appendices

None.